REMARKS

Entry of the foregoing and favorable reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment, claims 2, 11, 30 and 32 have been canceled and the subject matter of claims 11 and 30 have been incorporated into independent claims 1 and 24, respectively. Claims 1, 17 and 24 have been amended to further clarify the present invention. Claims 33 to 40 have been added. The newly added claims recite the method of or a kit for diagnosing synovial disease. These do not present new matter; this subject matter was already presented in the original elected claim set.

Prior to addressing the issues raised by the Examiner, Applicants would like to briefly discuss the background of the present invention. Claims 1 and 33 are directed to a method of diagnosing a synovial disease or monitoring the evolution of a synovial disease, respectively. Each method entails bringing a biological sample from an individual into contact, *in vitro,* with a means for measuring a specific marker for synovial disease, said specific marker being diglycosylated pyridinoline. Specific markers are defined in the specification at paragraph [0030] as meaning:

> "a substance or compound that can distinguish between a synovial disease and other diseases and in particular a bone and/or cartilage afflictions."

Thus, Applicants have discovered that by determining two pyridinoline glycosylation forms, specific markers for the degradation of the bone matrix, cartilage or synovia can be determined. For example, an increase in the amount of monosaccharide pyridinoline in a biological sample corresponds to degradation of collagen in the bone. An increase in the quantity of pyridinoline and the absence of glycosylated

pyridinoline corresponds to a degradation of collagen of cartilage origin, while an increase in the quantity of disaccharide pyridinoline corresponds to an increase in degradation of collagen of synovial origin.

Turning now to the Official Action, Claims 1, 2, 11, 13 to 19, 24, 30 and 32 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection should be rendered moot by the current claim amendments.

More specifically, claims 2 and 32 have been canceled. Claim 1 has been amended to recite a method of evolution of a disease. The diagnosis of a synovial disease has been deleted from claims 1 and 24 and is now the subject of claims 33-40.

Therefore, withdrawal of this rejection is respectfully requested.

Claims 1, 2, 11, 13-16, 18 and 19 have been rejected under 35 U.S.C. §103 (a) as being unpatentable over Blum et al in view of Robins (WO 89/12824). This rejection is respectfully traversed, including to the extent it would be applied prospectively to claims 33-40.

Blum et al disclose measuring the level of pyridinoline in synovial fluid samples originating from knee effusions in which the patients tested had various diseases ranging from osteoarthritis (OA) and rheumatoid arthritis (RA) to Crohns disease (involving one patient). Crohns disease is not an inflammatory joint disease. In the text of the publication, Blum et al states:

(1) Pyr is the major collagen cross-link in articular cartilage, bone and synovial fluid;

(2) Pyr and D-Pyr are the most sensitive urinary markers of bone resorption; and

(3) That Pyr and D-Pyr are increased in RA and OA (citing, *inter alia*, two publications authored by S.P. Robins, who is the named inventor on the secondary reference).

Blum et al do not mention any other marker. In particular, there is no suggestion that diglycosylated pyridinoline can be used as a specific marker for diagnosing synovial disease or monitoring the evolution of synovial disease.

Regarding claims 16 and 36, Blum et al teach that pyridinoline (hereafter Pyr) is in fact present in the synovial fluid and that the synovial fluid samples must be pooled in order to detect Pyr. Furthermore, Blum et al disclose that their procedure should not be used routinely for clinical purposes as disclosed in the last paragraph of this article, where the following is stated:

> This technique (HPLC) is not intended to be used routinely for clinical purposes…

Therefore, using the HPLC procedure described by Blum et al to monitor the evolution of a synovial disease or to diagnose a synovial disease is discouraged.

Robins, WO 89/12824, disclose a method for monitoring collagen degradation in bone and cartilage using mono- and disaccharide derivatives of hydroxylysine. More specifically the following is stated at page 6 of Robins' specification:

> Two types of tissue of particular interest are bone and cartilage. The presence of degradation of bone collagen alone is an indicator of osteoporosis and other bone disorders, while the presence of degradation of both bone collagen and cartilage collagen is an indicator of arthritic disorders or diseases (emphasis added).

Robins does not disclose that disaccharide derivatives of hydroxylysine can be used as a specific marker for diagnosing a synovial disease or monitoring the evolution of a synovial disease. On page 5, Robins teaches as follows:

> The relative proportion of mono- to disaccharide derivatives of hydroxylysine varies with different tissues. For the main tissues of interest (i.e. those that contain pyridinoline) cartilage contains almost

> entirely Gal.Glc, whereas in bone collagen the monosaccharide predominates (emphasis added).

Based on this disclosure, and particularly the teaching regarding cartilage and the Gal.Glc disaccharide derivative, Applicants submit that the skilled artisan would not have been motivated to use the disaccharide derivative of hydroxylysine as a specific marker for synovial disease. This is in contrast to the present invention wherein the diglycosylated pyridinoline is used as a specific marker for synovial disease (and not collagen degradation in cartilage). In fact it is the absence of glycosylated pyridinoline that is indicative of collagen degradation in cartilage (see, paragraph [0013] of the present specification).

Therefore, the collective teachings of Blum et al and Robins fail to render the presently claimed invention obvious. There is no teaching or suggestion in the collective prior art teachings that diglycosylated pyridinoline is a marker *specific for synovial disease* such that it can be used to distinguish this disease from bone and cartilage afflictions.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

Claim 17 has been rejected under 35 U.S.C. §103 (a) as being unpatentable over Blum and Robins et al in view of Sinigaglia. For the following reasons, this rejection is respectfully traversed.

Applicants' arguments regarding Blum et al and Robins set forth above are believed to be equally applicable to this rejection, and thus are incorporated herein as if they were explicitly repeated.

Sinigaglia et al teaches urinary and synovial pyridinium crosslinks in patients with rheumatoid arthritis and osteoarthritis. The Examiner cites this reference as disclosing that creatinin can be used as a standard reference. However,

the concentrations described in Sinigaglia et al are expressed as pmol/μmol of creatinin, which is equivalent to nmol/mmole of creatinin. However, Claim 17 recites nmol/nmol of creatinin at a range of about 5 nmol/nmol creatinin to about 9 nmol/nmol creatinin. Sinigaglia does not even suggest this range. Regardless, this publication does not remedy the deficiencies of the primary references. When considered alone or collectively with Blum and Robins, there is still no suggestion that would have motivated persons skilled in the art to produce the presently claimed invention with a reasonable expectation of success.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 24 and 30 have been rejected under 35 U.S.C. §103 (a) as being unpatentable over Blum et al in view of Robins and further in view of Boguslaski et al. As far as this rejection may pertain to the claims of record, this rejection is respectfully traversed.

Blum et al and Robins were discussed extensively above and the same arguments apply equally to this rejection and thus are incorporated herein.

Boguslaski et al describe a test kit device for determining the presence of *Helicobacter pylori*. There is no suggestion of a kit that contains materials that can diagnose synovial disease or monitor the evolution of synovial disease.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

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